Elbasvir/Grazoprevir (Zepatier™) Criteria for Use
February 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive this regimen without local adjudication.*

☐ HCV **genotype 2, 3, 5, or 6** infection
☐ Previous virologic failure to regimens containing an NS5A inhibitor (refer to Issues for consideration)
☐ Child-Pugh Class B or C decompensated liver disease (i.e., Child-Pugh score ≥7, MELD score ≥15, and/or clinical manifestations)
☐ Limited Life Expectancy (refer to issues for consideration)
☐ Documented ongoing nonadherence to prescribed medications or medical treatment, failure to complete hepatitis C virus (HCV) disease evaluation appointments and procedures or unable to commit to scheduled follow-up/monitoring for the duration of treatment
☐ Known hypersensitivity to elbasvir/grazoprevir (if applicable) or any other component of this direct acting antiviral based-regimen
☐ HIV/HCV co-infection where antiretroviral drug-interactions preclude the use of elbasvir/grazoprevir (Refer to Issues for Consideration and http://www.hep-druginteractions.org for a list of acceptable drugs)

Drug interactions

☐ Co-administration with drugs that are 1) strong CYP3A inducers (e.g., phenytoin, carbamazepine, rifampin) ; 2) OATP1B1/3 inhibitors (e.g., cyclosporine, darunavir, atazanavir, tipranavir, lopinavir or saquinavir) OR 3) efavirenz

When elbasvir/grazoprevir is used in combination with ribavirin:

☐ Contraindication and/or intolerance to ribavirin

- Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, and/or significant anemia (i.e. symptomatic or baseline hemoglobin <10g/dL) and/or history of *significant* adverse events with previous ribavirin-containing regimen. **Please note that history of anemia related to ribavirin-containing regimen should be evaluated in context of PBM CFU for ESA (i.e., ribavirin dose reduction to 600mg must have been instituted prior to consideration of ESA use) and does not necessarily constitute intolerance.

Inclusion Criteria *The answers to all of the following must be fulfilled in order to meet criteria.*

☐ **For HCV Genotype 1a patients, baseline testing for the presence of virus with specific NS5A resistance-associated polymorphisms (RAPs)** at the amino acid positions 28, 30, 31, or 93 **to guide elbasvir/grazoprevir regimen**
☐ **Hepatitis C Virus Genotype 1 or 4 infection**
☐ Treatment regimen and duration according to the dosage and administration section below
☐ Under care of and/or in collaboration with an experienced VA HCV practitioner
☐ Adherence counseling performed including laboratory follow-up and documented understanding by patient

For women of childbearing potential receiving ribavirin or who have a male partner receiving ribavirin

☐ When elbasvir/grazoprevir is used in combination with ribavirin therapy (which is pregnancy category X), it should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Two effective methods of contraception should be used during treatment with elbasvir/grazoprevir and concomitant ribavirin, and for 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during HCV therapy.

Dosage, Administration

Elbasvir/grazoprevir: One tablet taken orally once daily with or without food. For certain patient populations, co-administration with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day) is recommended. **Treatment regimen and duration are based upon patient characteristics as described in the Table below.**

Treatment Regimen and Duration for HCV Genotype 1 or 4 based upon patient characteristics

Population includes HCV monoinfection, HCV/HIV-1 co-infection, hepatocellular carcinoma (HCC) and patients with or without cirrhosis	**Dosage Regimens**	**Total Treatment Duration**
Genotype 1a: Treatment-naïve or treatment-experienced with PEG/RBV **without** baseline **NS5A** polymorphisms at the amino acid positions 28, 30, 31, or 93	Elbasvir/grazoprevir	12 weeks
Treatment-experienced with a first generation HCV protease inhibitor (e.g., telaprevir, boceprevir or simeprevir) in combination with PEG/RBV regimen **without** baseline **NS5A** polymorphisms at the amino acid positions 28, 30,	Elbasvir/grazoprevir plus RBV	12 weeks

31, or 93		
Genotype 1a: Treatment-naïve or treatment-experienced (including prior PEG/RBV or first generation HCV protease inhibitor ,e.g, telaprevir, boceprevir or simeprevir, in combination with PEG/RBV) **with** baseline **NS5A** polymorphisms at the amino acid positions 28, 30, 31, or 93	Elbasvir/grazoprevir plus RBV	16 weeks
Genotype 1b: Treatment-naïve or treatment-experienced with PEG/RBV	Elbasvir/grazoprevir	12 weeks
Treatment-experienced with a first generation HCV protease inhibitor (e.g., telaprevir, boceprevir or simeprevir) in combination with PEG/RBV regimen	Elbasvir/grazoprevir plus RBV	12 weeks
Genotype 4: Treatment-naïve	Elbasvir/grazoprevir	12 weeks
Treatment-experienced with PEG/RBV	Elbasvir/grazoprevir plus RBV	16 weeks

PEG/RBV: peginterferon/ribavirin

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving HCV therapy, the following monitoring is recommended for elbasvir/grazoprevir regimen:

- **Hematologic adverse events (anemia) if co-administered with ribavirin:** Complete blood count should be obtained at baseline and at treatment weeks 2, 4, and 8, and at other time points, as clinically appropriate. Initial management of anemia should consist of ribavirin dose reduction to 600mg for hemoglobin <10g/dL or sooner if clinically indicated; for additional monitoring and management of Hepatitis C treatment-related anemia refer to the PBM CFU for Recombinant Erythropoietin.
- **ALT Elevations:** Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12.
    - Patients should be instructed to consult their healthcare professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces**.**
    - Consider discontinuing elbasvir/grazoprevir if ALT levels remain persistently greater than 10 times the ULN.
    - Discontinue elbasvir/grazoprevir if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.
- **Careful virologic monitoring:** Patients should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.
- **Sustained Viral Response (SVR) or relapse** should be determined by measurement of HCV RNA at the end of therapy and 12 weeks thereafter.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.
- **Monthly pregnancy tests** for women of childbearing potential receiving ribavirin

Issues for Consideration

Treatment Considerations

- **Effect of Baseline NS5A Resistance on SVR12 in GT1a**

Baseline NS5A polymorphisms at resistance associated positions 28, 30, 31, or 93 were evaluated. Across all elbasvir/grazoprevir (EBR/GZR) Phase 2/3 studies, the prevalence of polymorphisms at any of these positions in genotype 1a patients in the US was 12% (37/309).

- The presence of one or more NS5A amino acid polymorphisms at position M28, Q30, L31, or Y93 was associated with reduced efficacy of EBR/GZR for 12 weeks, regardless of prior treatment history or cirrhosis status (refer to table). In clinical trials the effect of the following polymorphisms was most significant: M28A/G/T, Q30D/E/H/K/R, L31M/V, and Y93C/H/N

	EBR/GZR for 12 weeks SVR12	**EBR/GZR + RBV for 16 weeks SVR12**
No baseline NS5A polymorphisms (M28, Q30, L31, or Y93)	441/450 (98%)	49/49 (100%)
Presence of baseline NS5A polymorphism (M28, Q30, L31, or Y93)	39/56 (70%)	6/6 (100%)

- **Genotype 1 patients who had previous virological failure with regimen containing a NS5A inhibitor:** Elbasvir/grazoprevir regimen has not been studied and therefore, cannot be recommended. Patients who previously failed treatment with an NS5A inhibitor-containing regimen may have resistance-associated variants to currently available agents. Resistance testing is recommended to guide re-treatment options.
- **Genotype 1 patients who had previous virological failure with sofosbuvir+peginterferon+RBV or sofosbuvir+RBV**:

Elbasvir/grazoprevir has not been evaluated in this population.

- **ALT elevations:** In clinical trials, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the ULN, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in the following subpopulations: female sex (2% [10/608]), Asian race (2% [4/164]), and age 65 years or older (2% [3/177]).
- **Populations unlikely to benefit from HCV treatment:** According to AASLD/IDSA HCV Guidelines, "patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment. Chronic hepatitis C is associated with a wide range of comorbid conditions. Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence."

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- **HIV**: **Co-infected patients should be managed in consultation with an experienced HIV treatment provider. Due to potential drug interactions with antiretrovirals, alternative treatment with ledipasvir/sofosbuvir is recommended in patients where antiretroviral drug-interactions preclude the use of elbasvir/grazoprevir).** Potential antiretroviral regimens that can be co-administered with elbasvir/grazoprevir need to be carefully evaluated prior to initiation of the HCV regimen. Refer to http://www.hep-druginteractions.org for potential options.
- **Decompensated cirrhosis:** Elbasvir/grazoprevir is **contraindicated** in patients with decompensated cirrhosis (Child-Pugh B and C). Alternative treatment with ledipasvir/sofosbuvir plus ribavirin is recommended (refer to ledipasvir/sofosbuvir CFU).
- **Hepatocellular carcinoma (HCC) or other cancer:** It is reasonable to treat HCV in any patient with HCC or other malignancy *if there is a high likelihood that the cancer has been cured*. Curative treatments for solitary or early stage HCCs within Milan criteria include resection and thermal ablation as well as liver transplantation (TACE, radioembolization, radiation therapy and targeted/chemotherapy are NOT considered curative). For those receiving resection or thermal ablation, if staging studies indicate good likelihood of success (absence of macrovascular invasion, clear margins, etc.) and if follow-up restaging studies show no evidence of cancer recurrence, then treatment of HCV may be offered.
- **Dosage adjustment hepatic impairment:** No dosage adjustment in patients with mild hepatic impairment (Child-Pugh A); contraindicated in patients with moderate and severe hepatic impairment (Child-Pugh B and C).
- **Pre-Liver transplant (also see decompensated cirrhosis and HCC bullet above): The decision to treat *any* patient awaiting transplantation should be made in consultation with the transplant center where the patient is listed and determined on a case by case basis**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (pre- or post-) or whether treatment is appropriate given patient's prognosis.
- **Post-Liver Transplant:** Due to potential of significant interactions with immunosuppressants, alternative treatment with ledipasvir/sofosbuvir plus ribavirin is recommended to minimize potential for interactions (refer to ledipasvir/sofosbuvir CFU).
- **Renal Impairment:** No dosage adjustment is required in patients receiving elbasvir/grazoprevir with mild, moderate or severe renal impairment including hemodialysis. However, ribavirin is known to be substantially excreted by the kidney, and the risks of adverse reactions are greater in patients with impaired renal function. The total daily dose of ribavirin should be reduced for patients with creatinine clearance less than or equal to 50 mL/min as follows: creatinine clearance between 30-50ml/min use alternating doses of 200mg and 400mg every other day; for creatinine clearance <30ml/min or for hemodialysis use 200mg daily.
- **Substance or Alcohol Use**: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists as needed. **Thus, automatic disqualification of patients as treatment candidates based on a specific length of abstinence is unwarranted and is strongly discouraged**.
- **Mental Health Conditions:** HCV-infected patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. Patients should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.
- **Hepatitis B:** No safety and efficacy data are available in this population; prescribing information states that no dosage adjustments are needed in patients receiving tenofovir, entecavir or lamivudine when co-administered with the elbasvir/grazoprevir.

Drug-interactions (Refer to full prescribing information for details):

- Grazoprevir is a substrate of OATP1B1/3 transporters. Co-administration with drugs that inhibit OATP1B1/3 transporters may result in a significant increase in the plasma concentrations of grazoprevir.
- Elbasvir and grazoprevir are substrates of CYP3A and P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir appears to be minimal. Co-administration of moderate or strong inducers of CYP3A may decrease elbasvir and grazoprevir plasma concentrations leading to reduced therapeutic effect of elbasvir/grazoprevir. Co-administration with strong CYP3A inhibitors may increase elbasvir and grazoprevir concentrations.

Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use and limiting acetaminophen use to no more than 2g/day.
- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if appropriate.
- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site http://vaww.hepatitis.va.gov

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